IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Julie Straub, David Altreuter, Howard Bernstein, Donald E. Chickering, III, Sarwat Khattak, and Greg Randall		
Serial No.:	10/053,929	Art Unit:	1618
Filed:	January 22, 2002	Examiner:	Blessing M. Fubara
For:	*POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*		

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REPLY BRIEF TO EXAMINER'S ANSWER

Sir:

This is a Reply Brief to the Examiner's Answer mailed March 17, 2009, in the above-referenced application. A Request for Oral Hearing accompanies this Reply Brief. The Commissioner is hereby authorized to charge $1,080.00, the fee for Requesting an Oral Hearing for a large entity, to Deposit Order Account No. 50-3129.

Appellants respectfully point out that an Appeal Brief was filed on December 9, 2008 in response to the Office Action mailed October 16, 2008. However, the Examiner's Answer refers to the previous Appeal Brief filed July 9, 2007, which was filed in response to a prior Office Action mailed December 8, 2006.

It is believed that no additional fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(7) ARGUMENT

Appellants affirm all the arguments made in the Appeal Brief.

The Examiner has failed to establish a *prima facie* case of obviousness

The claims on appeal are directed to a method of making, not a composition

It appears that the Examiner is reviewing the claims as if they were drawn to a composition instead of a method of making. For example, the Examiner states, "it is noted that the goal of the process is the formation of a porous matrix and the end result of Unger's process is that a porous matrix is prepared". (Page 5 of the Examiner's Answer) The fact that the claimed method and method described in Unger may both produce porous matrices is irrelevant. The Federal Circuit has emphasized that each statutory class of claims should be separately considered, noting that claims to a compound are distinct from claims to a method for making the compound. "[A] process or method of making the compounds is a quite different thing; they may have been made by a process which was new or old, obvious or nonobvious" *In re Pleuddemann*, 910 F.2d 823, 827, 15 U.S.P.Q.2d 1738, 1740 (Fed. Cir. 1990). The obviousness analysis must focus on the differences between the claimed method and Unger's method.

Further, the claims on appeal are directed to a particular process for forming a porous matrix with particular properties, which are also specified in the claims. Unger only broadly

mentions diameters for the overall particles formed using its method (*see e.g.* Unger, para. 0204), but does not indicate other properties, such as the diameter of drug microparticles within the matrix, the TAP density of the overall particles, nor the total surface area of the overall particles. The Examiner has provided no evidence that the compositions prepared by the method described in Unger inherently has the properties specified in claim 16.

The differences between steps (a) and (b) of the claimed method and the steps of the method described in Unger differ in kind

The Examiner alleges that the claimed methods and the methods described in Unger differ only in the order of the steps, and therefore, the claimed methods are *prima facie* obvious over Unger (*see* page 12, first full paragraph of the Examiner's Answer). Applicants respectfully disagree. As discussed in the Appeal Brief (*see* pages 8-10 of the Appeal Brief), the differences between step (a) of the claimed method and the first step of the method in Unger are substantive. The claimed method requires formation of a drug solution. In contrast, Unger describes the formation of an emulsion in the form of random aggregates of drug and surfactant (*see* paragraph 0184). This is a difference in kind, not in order. Therefore, the Examiner has not established a *prima facie* case of obviousness over Unger. Further, the Examiner has failed to show why one of ordinary skill in the art would be motivated to modify Unger to arrive at the claimed methods since Unger explicitly discloses using a solvent in which the drug is only marginally soluble (*see* Unger, paragraph 0075).

The Examiner mischaracterizes step (b) of the claimed method (*see* page 5, lines 7 and 8 of the Examiner's Answer). Step (b) of claim 16 specifies adding the solid pore forming agent to the drug solution to form a second solution, a suspension or an emulsion. Step (b) does not change the nature of the drug solution formed in step (a); the drug is still **dissolved** in the organic solvent. The pore-forming agent is suspended in the drug solution (*i.e.*, forming a suspension) or dispersed as droplets in the drug solution (*i.e.*, forming an emulsion) (*see* page 21, lines 23-31 of the application as filed). The drug does not precipitate from solution upon addition of the pore-forming agent. Unger requires the drug to be suspended in the solvent at all times. Therefore, step (b) also differs in kind from the steps in the method described in Unger.

Further, the Examiner has failed to show why one of ordinary skill in the art would modify the teachings of Unger to arrive at the claimed methods.

The Examiner's reliance on Gordon is unclear

The Examiner relies on U.S. Patent No. 5,976,574 to Gordon, which the Examiner characterizes as a "teaching reference", for the notion that claimed method steps are known in the art for the production of powder formulations. The Examiner explicitly states that Gordon is not relied on for the rejection over Unger. However, the Examiner points to Gordon as the basis for the motivation to modify the methods of Unger to arrive at the claimed methods (*see* pages 3 and 6 of the Examiner's Answer). The Examiner's purpose for citing Gordon is unclear to Appellants.

Gordon describes preparing a drug powder by dissolving a hydrophobic drug in a solvent to form a drug solution, suspending a hydrophilic excipient in the solution, and then spray drying the solution to form particles (Gordon, col. 4, lines 12-17). Gordon's method requires different steps than Unger's. Specifically, Unger clearly discloses that the active agent is suspended in the solvent, not dissolved. Therefore, one of ordinary skill in the art could not take steps from Gordon and merely substitute them into Unger's method. Further, Unger teaches away from such a substitution. Unger states "[T]he therapeutic is typically only marginally soluble in the solvent." (Unger, paragraph 0075). Unger discloses that the drug is suspended in a solvent to form a suspension or an emulsion. Thus, Unger teaches away from the methods described in Gordon. Therefore, one of ordinary skill in the art would not be combine Unger's method with Gordon's method to arrive at the claimed method.

Unger's teaching of incorporating an oil is in the context of effecting solubilization of the blowing agent

The Examiner alleges that Unger teaches solubilizing the drug in an oil (*see* page 5 of the Examiner's Answer). However, the Examiner's allegation regarding the use of an oil to solubilize the drug is taken out of context and is incorrect. Unger's statement regarding the use of an oil to effect solubilization follows the disclosure that the "[b]lowing agent is stabilized by the surfactant, such as a phospholipid or a fluorosurfactant, within aqueous or organic media, the former being preferred. Additionally, some non-polar drug emulsions may contain an oil to effect solubilization" (Unger, paragraph 184). Taken in context, this statement suggests that an

oil can be added to solubilize the blowing agent, not the drug. Thus, contrary to the Examiner's allegation, Unger does not disclose forming a drug solution.

The formation of a solution or suspension depends not only on the properties of the solvent, but on the properties of the drug as well

The Examiner mischaracterizes the scope of the claimed methods. The claims do not require **any** organic solvent as alleged by the Examiner (*see* page 5 of the Examiner's Answer), rather the claims recite a method requiring mixing a drug and an organic solvent to form a drug solution. The ability to form a drug solution is dependent on the properties of both the solvent **and** the drug. Likewise, with respect to the compositions in Unger, the ability to form an emulsion is dependent on the properties of the drug, solvent, and surfactant. Thus for a given drug, Unger's method requires the use of a solvent that will form an emulsion with the drug and surfactant. In contrast, even if the same drug is used, the claimed method requires a solvent that forms a solution.

Unger does not disclose or suggest adding a volatile solid pore forming agent to the drug solution and then removing the volatile solid pore forming agent

Unger describes methods of making the particles described therein beginning at paragraph 181. The pores in Unger's compositions are formed by the addition of a blowing agent, methylene chloride, which is a volatile liquid. Unger discloses that in the case of spray drying, "the emulsion or colloidal suspension is placed into association with a blowing agent, such as methylene chloride. As the suspension or emulsion is then spray dried, the drug dries

and the blowing agent and solvent are removed tending to form microcavities within the drug crystals." (Unger, paragraph 0184). The Examiner cites this passage as support for her allegation regarding the use of solid pore-forming agents (page 7, lines 1 and 2 of the Examiner's Answer). However, as discussed in the Appeal Brief (*see* pages 11 and 12 of the Appeal Brief), this statement is in the context of using liquid blowing agents, such as methylene chloride.

The use of a blowing agent, such as methylene chloride, rather than a volatile solid pore forming agent, is supported by the disclosure in paragraph 0013 of Unger that "the composition **optionally** contains a gas or gaseous precursor" (emphasis added) and paragraphs 0076 and 0184, which describe removing the liquid blowing agent to form a porous matrix. The fact that the solid gaseous precursor component is optional is evidence the gas or gaseous precursor cannot be used as a pore forming agent. Rather, Unger's method **requires** the addition of a liquid blowing agent, such as methylene chloride, which forms pores during drying. Further, paragraph 0176 explains that the gaseous precursor releases gas in the pores that were previously formed in the matrix. Unger does not disclose or suggest the use of solid pore-forming agents as required by the claimed method, nor has the Examiner demonstrated that one would be motivated to modify Unger to arrive at the claimed methods.

For at least the reasons discussed herein and in the Appeal Brief, claims 16-21 and 34 are not obvious over Unger, alone or in combination with Gordon.

For the foregoing reasons, Appellant submits that claims 16-21 and 34 are patentable.

Respectfully submitted,

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